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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/627,206	07/27/2000	Jane A. Gross	98-75C2	1238

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ZYMOGENETICS, INC.
INTELLECTUAL PROPERTY DEPARTMENT
1201 EASTLAKE AVENUE EAST
SEATTLE, WA 98102-3702

EXAMINER

ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
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1645

MAIL DATE	DELIVERY MODE
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12/07/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/627,206

Applicant(s)

GROSS, JANE A.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 107-111 and 117-132 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 107-111 and 117-132 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 9-21-2007 has been entered.

The amendment and response filed on 9-21-2007 are acknowledged. Claims 107, 110-111, 117 and 120-121 have been amended. Claims 89 and 102-106 have been canceled. Claims 122-132 have been added. Claims 107-111 and 117-132 are currently under examination.

Claim Objections Withdrawn

The objection to claims 107 and 117 for containing the phrase "consisting amino acid..." is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 89, 102-103, 105-106, 108 and 110-111 under 35 U.S.C. 102(a) as being anticipated by Bram et al. (WO 98/39361) is withdrawn in light of the amendment thereto.

The rejection of claims 89, 102-103, 105-106, 108 and 110-111 are rejected under 35 U.S.C. 102(e) as being anticipated by Bram et al. (U.S. Patent 5,969,102 – IDS-5) is withdrawn in light of the amendment thereto.

The rejection of claims 89 and 102-6 and 108-111 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of the amendment thereto.

The new matter rejection of claims 89, 102-111 and 117-121 under 35 U.S.C. 112, first paragraph, based on the limitation "a ligand binding fragment of a soluble form of a ztnf4 receptor..." in claim 89 is withdrawn. Cancellation said claim has rendered the rejection moot.

The new matter rejection of claims 89, 102-111 and 117-121 under 35 U.S.C. 112, first paragraph, based on the limitation "the first portion of the fusion protein comprises a ligand binding fragment of a soluble form of an extracellular domain of a ztnf4 receptor..." in claim 102 is withdrawn. Cancellation said claim has rendered the rejection moot.

The new matter rejection of claims 89, 102-111 and 117-121 under 35 U.S.C. 112, first paragraph, based on the limitation "wherein the TACI polypeptide has an amino acid sequence consisting of amino acid residues 25 to 104 of SEQ ID NO:6." in claim 107 is withdrawn in light of the amendment thereto.

The new matter rejection of claims 89, 102-111 and 117-121 under 35 U.S.C. 112, first paragraph, based on the limitation "wherein the TACI polypeptide has an amino acid sequence consisting of amino acid residues 1 to 154 of SEQ ID NO:6." in claim 117 is withdrawn in light of the amendment thereto.

The rejection of claim 102 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "an extracellular domain of a ztnf4 receptor" is withdrawn. Cancellation of said claim has rendered the rejection moot.

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The rejection of claim 107 and 117 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "consisting of the amino acid residues X to Y of SEQ ID NO:6." is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to methods of inhibiting B cell proliferation by the administration of by the administration a composition comprising a fusion protein that consists of a first and second portion joined by a peptide bond wherein the first portion

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consist of the amino sequence of amino acid 25 to 104 of SEQ ID NO:6 or residues 1 to 154 of SEQ ID NO:6 and wherein the second portion is a heavy chain constant region of human immunoglobulins (e.g. IgG1) and wherein said fusion protein binds ztnf4. Additionally, said composition may comprise multiple polypeptide fusions.

Claims 107-111 and 117-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bram et al. (WO 98/39361 – IDS-5), as cited above, in view of Presta et al. (U.S. Patent 5,739,277) is maintained for reasons set forth in the previous Office action in the rejection of claims 89 and 102-6 and 108-111.

Applicant argues:

1. Bram does not disclose the specific use for constructs comprising amino acids residues 25-104 or 1-154 of TACI.
2. Presta does nothing to remedy the failure of Bram.

Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokin α , BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see page 24, lines 24-26). Moreover, Bram et al. disclose that the “subunits” of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see page 20, line 1). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular

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domain (see page 18, lines 27-30). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see page 8, lines 1-6). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. hence Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds BLYS. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand). Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 110-111 and 120-121, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Bram et al. differs from the claimed invention in that they do not disclose the specific use of IgG1 heavy chains in fusion proteins or TACI extracellular sub-fragments consisting of amino acid residues 25-104 or 1-154 of SEQ ID NO:6 in fusion proteins.

However, given that there Bram discloses the use of the full length TACI extracellular domain (SEQ ID NO:6) and that there are a finite number of fragments of said extracellular domain and it would have been obvious to the skilled artisan to produce said fragments in order

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to identify the specific binding domain (fragment) of the TACI extracellular domain responsible for the observed biological activity (i.e. modulating B cell proliferation/activity). The skilled artisan would have had a reasonable expectation of success as the generation of protein fragments to identify biologically active domains [see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007)]

Presta et al. disclose methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)[see column 5, lines 48-55]. Presta et al. further disclose that the Fc portions of the various immunoglobulins have an increased circulatory half-life (see abstract and column 11, lines 63-65). Presta et al. teach that the Fc portions of the various immunoglobulins can be used interchangeably (see column 7, lines 3-45)

It would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. One would have been motivated to do so in order to achieve the expected result of generating TACI/Fc fusions functional in the methods disclosed by Bram et al. that have the increased circulatory half-life as disclosed by Presta et al.

Based on the state of the art and the teachings of the cited art, and absent of any evidence to the contrary, there would have been a reasonable expectation of success in combining the disclosure of Bram et al. with that of Presta et al. to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram et al.

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Claims 107-111 and 117-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bram et al. (U.S. Patent 5,969,102), as cited above, in view of Presta et al. (U.S. Patent 5,739,277) is maintained for reasons set forth in the previous Office action in the rejection of claims 89 and 102-6 and 108-111.

Applicant argues:

1. Bram does not disclose the specific use for constructs comprising amino acids residues 25-104 or 1-154 of TACI.
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Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokin α , BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see column 17, lines 16-18). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see column 13, line 64). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI (SEQ ID NO:6) and that the ligand binding region is a sub-fragment of the extracellular domain (see column 13, lines 7-12). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see column 5, lines 45-53). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit B cell proliferation,

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even though its identity is not known since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. hence Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds BLyS. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand). Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 110-111 and 120-121, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Bram et al. differs from the claimed invention in that they do not disclose the specific use of IgG1 heavy chains in fusion proteins or TACI extracellular sub-fragments consisting of amino acid residues 25-104 or 1-154 of SEQ ID NO:6 in fusion proteins.

However, given that there Bram discloses the use of the full length TACI extracellular domain (SEQ ID NO:6) and that there are a finite number of fragments of said extracellular domain and it would have been obvious to the skilled artisan to produce said fragments in order to identify the specific binding domain (fragment) of the TACI extracellular domain responsible for the observed biological activity (i.e. modulating B cell proliferation/activity). The skilled artisan would have had a reasonable expectation of success as the generation of protein

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fragments to identify biologically active domains [see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007)]

Presta et al. disclose methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)[see column 5, lines 48-55]. Presta et al. further disclose that the Fc portions of the various immunoglobulins have an increased circulatory half-life (see abstract and column 11, lines 63-65). Presta et al. teach that the Fc portions of the various immunoglobulins can be used interchangeably (see column 7, lines 3-45)

It would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. One would have been motivated to do so in order to achieve the expected result of generating TACI/Fc fusions functional in the methods disclosed by Bram et al. that have the increased circulatory half-life as disclosed by Presta et al.

Based on the state of the art and the teachings of the cited art, and absent of any evidence to the contrary, there would have been a reasonable expectation of success in combining the disclosure of Bram et al. with that of Presta et al. to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram et al.

New Grounds of Rejection
Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 107-109, 117-119 and 122-123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 11/748,978. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims sets encompass the use of fusion proteins comprising fragments of the extracellular domain of TACI. It should be noted that while the instant claims are drawn to a method of inhibiting B cell proliferation and the copending claims are drawn to methods of treating rheumatoid arthritis, both methods produce the same results as the inhibition of BlyS activity necessarily results in the inhibition of B cell proliferation and consequently the treatment of rheumatoid arthritis. Moreover, instant claim 123

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is specifically drawn to treating rheumatoid arthritis through the application of fusion proteins comprising the extracellular domain of TACI.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read "Robert A. Zeman". The signature is stylized with a large, sweeping initial "R" and "Z".

ROBERT A. ZEMAN
PRIMARY EXAMINER

December 3, 2007